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Anesthetizing the Fibrillating Heart

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There is increasing interest in neuromodulation as an antiarrhythmic therapy. The autonomic nervous system plays a prominent role in the regulation of normal cardiac physiological feature and is composed of a hierarchy of extrinsic and intrinsic components.[1] Extrinsic components are housed within the central nervous system and the intrathoracic extracardiac ganglia. Interventions that have been performed on the extrinsic components for the treatment of cardiovascular disease include cervical vagus nerve stimulation (VNS) for heart failure and stellate ganglionectomy for refractory ventricular arrhythmia.[2,3]

The intrinsic cardiac nervous system (ICNS) is composed of a complex network of neurons at the level of the heart, organized in ganglionated plexi (GPs) that are located in epicardial fat pads. These GPs are found at the atria, primarily around the pulmonary veins, and around the base of the aorta and pulmonary trunk and contain a mixture of cell bodies and axons of afferent, parasympathetic, and sympathetic efferent or interconnecting neurons.[1,4] The role of ICNS at the level of the heart in the initiation and maintenance of atrial fibrillation (AF) has been a subject of ongoing investigations. Canine models of AF demonstrate an increase in ICNS activity before AF episodes,[5] and, in humans, changes in autonomic tone before AF episodes, as determined by heart rate variability analyses, further support the role of the autonomic nervous system in human AF.[6] Carlson et al demonstrated that stimulation of the right atrial GP in human patients could induce sinus slowing,[7] and a subsequent study showed that right atrial GP stimulation affects atrial conduction times.[8] In addition to imposing changes in atrial electrophysiological features, stimulation of ganglia in the fat pad by the right superior pulmonary vein facilitates AF inducibility in canine hearts by providing a substrate for pulmonary venous firing to result in AF.[9] Following from these studies, interventions of the ICNS in AF have been explored. In a canine model, Schauerte et al showed that radiofrequency ablation via an endocardial approach could target atrial parasympathetic nerves to inhibit vagally mediated AF.[10] Subsequent study in human patients with AF illustrated that adjunctive GP ablation with catheter-based AF ablation resulted in higher success rates.[11] More recently, intraoperative injection of botulinum toxin type A has been studied for mitigation of risk of postcardiac surgery AF.[12,13]

These prior studies evaluated neuromodulation of GPs in patients with paroxysmal AF or in those who were at risk for postoperative AF. In this issue of the *Journal of the American Heart Association* (*JAHA*), Lee et al investigate whether injections of neuronal blocker lidocaine into the epicardial fat pads of patients with persistent and long-standing persistent AF affect atrial electrophysiological features.[14] To determine efficacy, the investigators first injected lidocaine into the epicardial fat pads of dogs during sinus rhythm and found that AF could no longer be induced in 4 of the 7 dogs in a VNS AF model. Subsequently, in 6 patients with persistent or long-standing AF undergoing coronary artery bypass grafting or valvular surgery, epicardial fat pads were injected with lidocaine. Electrograms were recorded across the atria using an electrode array and were characterized by shorter left than right atrial mean cycle lengths at baseline, with a left-right dominant frequency gradient. Although AF persisted in all patients after lidocaine injection, the left atrial cycle lengths prolonged with disappearance of the left-right dominant frequency gradient.

The investigators provide important evidence that modulating the GPs exerts effects on atrial electrophysiological features in human AF. Although studies evaluating adjunctive GP ablation or botulinum toxin injection reported outcomes on freedom from AF,[11–13] this study is unique in providing real-time evidence of GP involvement in atrial electrophysiological features while in AF. As the investigators point out, this finding is consistent with the loss of

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left-right frequency gradient observed with AF ablation.[15] However, it remains to be seen how successful such an approach would be in patients with persistent forms of AF and who may have significant electrical and structural remodeling of cardiac tissue. In this study, no patients had conversion to sinus rhythm with lidocaine injections at the GPs, and whether fine-tuning the neuromodulatory strategy could bring about successful treatment of AF is an unanswered question.

The ideal approach to neuromodulation of GPs is unclear. Acute ischemia and myocardial infarction studies in canine models have indicated that GP ablations may affect ventricular electrophysiological features to increase ventricular arrhythmia inducibility.[16,17] In humans, the AFACT (Atrial Fibrillation Ablation and Autonomic Modulation via Thoracoscopic Surgery) study raised concerns about radiofrequency ablation of major GPs.[18] In this prospective, randomized controlled study, patients with long-standing AF, enlarged atria, or failed catheter ablation underwent epicardial ablation of the 4 major GPs and the ligament of Marshall GP group at time of thoracoscopic AF surgery. However, not only did GP ablation fail to reduce AF recurrence, but it was also associated with increased adverse events. Most notably, 10% of the patients in the GP ablation group sustained sinus node dysfunction, half of whom required pacemaker implantation, compared with 3% in the placebo group. The unintended consequence of affecting sinus node function may have been caused by off-target ablative effects on the myocardium (or perhaps injury to the ICNS), and the authors conclude that a neuroablative strategy using radiofrequency energy should not be adopted in such patients. In contrast to these results, endocardial catheter ablation of the 4 major GP groups has had promising results in the treatment of sinus bradycardia, particularly in younger patients.[19] Additional study will be required to determine the exact role of neuroablation at the level of the heart.

If a neuromodulatory approach through chemical means proves advantageous, the ideal agent is unknown. Reassuringly, in contrast to the AFACT study, none of the patients in the 2 studies on botulinum toxin injections in the GPs developed sinus node dysfunction. However, the 2 studies yielded disparate results, with one showing sustained reduction in AF rates while the other showed no discernible difference in freedom from AF[12,13]; the reason for the differing results is unclear. Understanding the physiological features and the elements of the GPs that should be targeted may help guide the ideal neuromodulatory agent. In particular, GPs contain axons “en passant” to other regions of the heart and neuronal cell bodies with connections to not only the myocardium but also other neurons within cardiac ganglia and interganglionic connections. Use of a ganglionic blocker in place of the axonal blocker lidocaine may delineate which aspect of the GP modification provides benefit and may help tailor the intervention. For example, using such an approach, Fee et al were able to show differential effects of VNS when using a ganglionic versus an axonal blocker.[20] In a canine model, these investigators showed that injection of ganglionic blocker C6 had little effect on sinus slowing or atrioventricular block with cervical VNS. In contrast, injection of axonal blocker lidocaine resulted in a reduction in the atrioventricular block during left cervical VNS. Detailed studies such as this may discern whether neuromodulation targeting neuronal cell bodies or axons of passage are required to bring about a desired effect and whether such an approach could mitigate off-target effects.

The current study highlights that neuromodulation of the ICNS affects atrial electrophysiological features in a manner akin to that of AF ablation. Whether these findings can be extended as a treatment for AF without the off-target effects of radiofrequency ablative techniques remains to be seen. Identifying the components of the GPs involved in the pathogenesis of AF and understanding the functional significance of cardiac neuroanatomical features could promote the development of a targeted therapeutic strategy for AF.

Disclosures

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